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FALK, ANNE MARIE	

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NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/776,780	DURING, MATTHEW J.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-12 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-12 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed October 12, 2007 (hereinafter referred to as "the response") has been entered. Claims 1, 2, and 4-12 have been amended and Claims 15, 16, 18, and 19 have been cancelled.

Accordingly, Claims 1, 2, 4-12, and 14 remain pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 12, 2007 has been entered.

With the exception of Figure 4A, the objections to the drawings are withdrawn in view of the cancellation of Figures 3A-3C, 4B-4K, 8A-8I, 8K-8M, 9A-9L, 10A-10I, and 11A-11I, and the amendment of Figures 3D-3E, 8J, 12A-12D, and 13. Figure 4A remains objected to for the reasons set forth below.

The objections to the specification are withdrawn in view of the amendments to the specification at pages 2-16 of the response.

The rejection of Claims 2, 5, 6, 11, 12, 14, 15, 16, 18, and 19 under 35 U.S.C. 112, second paragraph, for indefiniteness in their recitation of "neurological disorder" is withdrawn in view of the amendments to Claims 2, 5, 6, 11, and 12 to remove the phrase "neurological disorder" and in view of the cancellation of Claims 15, 16, 18, and 19.

The rejection of Claims 2, 5, 6, 12, 14, and 15 under 35 U.S.C. 112, second paragraph, for indefiniteness in their recitation of "target protein" in conjunction with "an N-methyl-D-aspartate (NMDA) receptor antigen" is withdrawn in view of the amendments to Claims 2 and 12 to replace the term "target protein" with "an NMDA receptor" and in view of the cancellation of Claim 15.

The rejection of Claims 16, 18, and 19 under 35 U.S.C. 112, second paragraph, for indefiniteness in their recitation of "comprising genomic DNA of an N-methyl-D-aspartate (NMDA) receptor antigen" is withdrawn in view of the cancellation of Claims 16, 18, and 19.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 120 is acknowledged. However, the provisional applications and parent application upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for Claims 1, 2, 4-12, and 14 of this application, for the same reasons discussed hereinbelow as applied to the present application. Application serial nos. 60/116,748, 60/127,142, and parent application no. 09/491,896 fail to provide an enabling disclosure for the invention now being claimed in Claims 1, 2, 4-12, and 14, for the reasons discussed herein below as a rejection under 35 U.S.C. 112, first paragraph, as applied to the instant application.

Thus, the earlier-filed applications do not meet the requirements under 35 U.S.C. 119(e) and 120 for the benefit of obtaining priority to an earlier-filed application.

Accordingly, the Lissin et al. (June 1998) reference is applied as a 102(b)-type reference.

Claim Objections

Claims 2, 5, 6, and 10 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in

independent form. Claims 2, 5, 6, and 10 are directed to the composition of Claim 1 with no further structural limitations. The claims recite additional functional language, but the functions recited are inherently present in the composition of Claim 1 and therefore Claims 2, 5, 6, and 10 are identical in scope to Claim 1, which is not permitted. The functional language imparts no further structural limitations on the claimed composition.

Claims 1, 2, 4-12, and 14 are objected to because of the following informalities: the phrase "a pharmaceutical acceptable carrier" is not grammatically correct. Amending the claims to recite "a pharmaceutically-acceptable carrier" would be remedial. Appropriate correction is required.

Double Patenting

Applicant is advised that should Claim 12 be found allowable, Claim 11 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, the method of Claim 11 requires the single active step of administering the composition of Claim 1 to a subject. Claim 1 is directed to a composition comprising a vector comprising a nucleic acid sequence encoding N-methyl-D-aspartate (NMDA) receptor antigen, and a pharmaceutical carrier. The method of Claim 12 requires the same single active step as that of Claim 11 – administering a composition comprising a vector comprising a nucleic acid sequence encoding N-methyl-D-aspartate (NMDA) receptor antigen and a pharmaceutical carrier.

Drawings

In the amendments to the drawings filed October 12, 2007, Figures 4B-K were cancelled.

Figure 4A remains objected to under 37 CFR 1.83(a) because the drawings are not numbered consecutively. The next consecutive number after Figure 4A would be Figure 4B, not Figure 5A. Figure 4B has been cancelled by the amendment of October 12, 2007. Absent a Figure 4B, Figure 4A should be re-labeled as Figure 4. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). The label should be placed in the top margin (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because of the following informalities: the specification refers to figures having features that are not depicted in the drawings and/or not visible in the drawings. At page 67 the specification refers to images that are pseudocolored according to fluorescent intensity and further refers to a transition from red to yellow. However, the drawings are in black and white and therefore the colored features are not depicted.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-12, and 14 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record set forth in the Office Actions of 11/21/05 and 11/30/06 and for the reasons set forth below, because the specification, while being enabling for (i) a composition comprising an AAV vector comprising a nucleic acid encoding NMDAR1 operably linked to a promoter and (ii) a method of ameliorating brain damage associated with epilepsy or stroke in a rat, via prior oral administration of said AAV vector, such that the antigen is expressed and elicits production of NMDAR1-specific antibodies in the circulatory system of the rat, wherein epileptic seizures are diminished and stroke infarct volume is decreased as compared to an untreated control rat, does not reasonably provide enablement for a composition comprising any vector encoding any NMDA receptor antigen, nor for a method of modulating or delaying onset of epilepsy, stroke, or decreased cognition in any subject, by administration of any vector encoding any NMDA receptor antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of enablement set forth above is not intended to suggest specific claim language, but rather is intended to advise Applicant of the broadest scope that is considered to be enabled. It is Applicant's responsibility to identify claim language that is properly supported in the specification and that falls within the scope acknowledged to be enabled.

At page 22 of the response, Applicant asserts that Claim 1 recites a composition, not a treatment, and therefore Applicant disagrees with the Examiner's statement that "the claims continue to cover

treatment of any neurological injury or disease." Applicant notes that amended Claim 1 recites a composition, not a treatment. Accordingly, Applicant alleges that Claim 1 does not recite its potential uses. On the contrary, although Claim 1 has been amended to delete the phrase "thereby providing neuroprotection to the subject," the claim continues to recite the functional language "such that the expressed antigen elicits production of antibodies in a circulatory system of the subject, wherein the antibodies pass across a blood-brain barrier into a central nervous system upon injury or disease." As such, the specification must provide enablement for the full scope of the functional language. However, there is no evidence that antibodies would cross the blood-brain-barrier (BBB) over the full scope of any injury or disease. For example, an injury to the foot would not be expected to alter the permeability of the BBB and therefore the claimed composition is not enabled over the full scope for this intended use, i.e. to cause NMDA receptor-specific antibodies to enter the central nervous system (CNS) over the broad scope of any disease or injury as set forth in the claims. Likewise, there is no evidence that Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), dementia, or depression alter the permeability of the BBB to allow antibodies to pass into the CNS. The specification contemplates that the claimed invention will ameliorate or prevent the onset of a neurological disorder in a subject. The specification further states that "the disorder is selected from the group consisting of epilepsy, stroke, Alzheimer's, Parkinson's, dementia, Huntington's disease, amyloid lateral sclerosis and depression," (page 3, lines 9-12) but there is no evidence that all these diseases will alter the permeability of the BBB to allow antibodies to pass into the CNS. Although Example 6 shows that kainate administration increases the permeability of the BBB, allowing the detection of IgG in the hippocampus of vaccinated rats (page 71 of specification), there is no evidence that epilepsy or epileptic seizures alone, in the absence of kainate, causes increased permeability of the BBB so as to allow antibodies to enter the CNS. The instant specification does not provide specific guidance teaching which conditions will

sufficiently compromise the BBB to the extent that sufficient amounts of antibodies are able to cross and produce the desired effect.

Claims 11 and 12 have been amended to recite "ameliorating or delaying onset of epilepsy, stroke, or decreased cognition" but there is no evidence that administration of an NMDA receptor vaccine will ameliorate or delay the decreased cognition associated with aging, Alzheimer's disease, or any other cause. Given the unpredictability in the art of genetic immunization, the skilled artisan would have been required to engage in undue experimentation to ameliorate or delay the onset of decreased cognition associated with any underlying cause, by administration of a vector encoding an NMDA receptor.

Claim 12 recites that the antibodies produced modify the function of an NMDA receptor in the central nervous system. In the context of receptors, the term "modify" covers both the stimulation/agonism and inhibition/antagonism/blocking of the receptor. However, the instant specification only teaches how to raise antagonistic antibodies that block and inhibit the function of the NMDA receptor. Thus, the specification fails to both describe and enable methods that elicit antibodies that stimulate the NMDA receptor. Accordingly, the specification fails to enable the full scope of the claim.

At page 22 of the response, Applicant asserts that the method does not have to be able to cure the disorders and that evidence of regression is not necessary for enablement. First, as regards cure, there is nothing in the enablement rejection pertaining to cure. Second, as regards evidence of regression, the method claims do recite "ameliorating or delaying onset of epilepsy, stroke, or decreased cognition" and therefore enablement does require that one skilled in the art would be able to predictably achieve these effects without undue experimentation. The claimed invention recites claim-designated effects that must be enabled by the specification. Applicant goes on to claim that *in vivo* or clinical data is not necessary for patentability analysis. However, there is nothing in the enablement rejection suggesting that *in vivo* or clinical data is required. A complete *Wands* analysis has been provided, with a discussion of those factors

most relevant to the present claims, including the nature of the invention, the state of the prior art, the predictability of the art, the breadth of the claims, the amount of direction or guidance presented, the presence or absence of working examples, and the quantity of experimentation necessary to enable the claims over their full scope. Giving due consideration to all the *Wands* factors, it was concluded that the specification fails to provide an enabling disclosure for the full scope of the claims. Numerous references were provided pointing to the unpredictability in the art of DNA vaccination and it is maintained that the specification fails to enable the full scope of the claims.

At page 22 of the response, Applicant refers to page 9 of the Office Action of 11/21/05 and asserts that there is no requirement that the claimed invention be "ideal" or that it should achieve "true success." However, the prior Office Action makes no mention of an ideal vaccine or factors that would make a vaccine ideal. On the contrary, factors recited are those that would make a gene-based therapy workable, i.e. sufficient to produce a therapeutic effect. Applicant goes on to assert that the claimed invention is enabled even if the claims encompass inoperative subject matter. While inoperative embodiments are permissible, a claim is not enabled when a skilled artisan cannot readily distinguish the operative embodiments from the inoperative embodiments using nothing more than routine experimentation. It is well established in our law that the specification must enable the full scope of the claims. Given the *Wands* analysis of record, the specification fails to enable the full scope of the claims.

At page 23, paragraph 2 of the response, Applicant asserts that, in the area of gene therapy, a great number of successes have been documented. Applicant points to Verma et al. (1997) for stating that "adenoviral vectors are extremely useful if expression of the transgene is required for short periods of time" and Shoji et al. (2004) for guidance on oligonucleotides. However, the instant claims are not directed to the use of oligonucleotides and there is no evidence that adenoviral vectors would provide expression sufficient to produce antibodies that antagonize the NMDA receptor in the CNS. Given the lack of predictability in the art, the skilled artisan would be required to engage in undue experimentation

to enable the full scope of the claims because the skilled artisan would be required to engage in trial-and-error experimentation to test an enormous variety of vectors across an enormous variety of conditions, given the very large number of parameters that can be varied within the scope of the claims, such as route of administration, dosage, type of vector, regulatory elements driving expression of the receptor, etc.

At page 23, paragraph 3 of the response, Applicant points to McCluskie et al. (1999) for suggesting that "it is probably safe to say that any vaccine that works in a human will work in a mouse." Applicant neglected to quote the most important part of the statement which makes the author's point which is "but not necessarily vice versa." Thus, it is abudantly clear that those of skill in the art do not accept that immune responses produced in rodents are predictive of immune responses that may be achieved in humans. McCluskie is clear and unequivocal about this lack of predictability. The entire statement is as follows:

> In summary, mice may have limited value for choosing the best route of DNA vaccine delivery for humans. While efficacy in murine models has preceeded the successful development of many human vaccines, it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa. Therefore, it is difficult to predict from mouse studies the potential of a new vaccine for humans. In fact, in those human trials that have been carried out, none of the DNA vaccines induced the strong immune responses that had been seen in mice with the same vectors. (page 296, column 2, last paragraph).

At page 23, paragraph 4 of the response, Applicant refers to Babiuk (1999) for stating that "expression of the foreign gene in vivo should lead to an immune response to the protein produced by the gene." Applicant is reminded that the claimed invention is not directed to raising an immune response to a protein from a foreign gene, but rather is directed to raising an immune response to a self protein, which is considerably more difficult given the tolerance to self antigens, limited modes of antigen presentation, and limited routes of administration suitable for raising an antibody response to a self protein.

At page 24, paragraph 1 of the response, Applicant objects to the argument that only oral administration is enabled, stating that "[e]ven if it is scientifically sound to doubt the viability of other, non-exemplified administrative routes, the claimed invention remains enabled, because the claims may

encompass 'inoperative subject matter.'" As discussed above, while inoperative embodiments are permissible, a claim is not enabled when a skilled artisan cannot readily distinguish the operative embodiments from the inoperative embodiments using nothing more than routine experimentation. It is well established in our law that the specification must enable the full scope of the claims. Given the *Wands* analysis of record, the specification fails to enable the full scope of the claims. The court has stated that "[n]aturally, the specification must teach those of skill in the art how to make and use the invention as broadly as it is claimed." *In re Goodman*, 29 USPQ2d 2010 at 2013 (Fed. Cir. 1993). Citing Examples 2-6, Applicant goes on to allege that the specification gives numerous examples of how to demonstrate that the claimed invention is operative. On the contrary, the teachings of Examples 2-6 are limited to oral administration of an AAV vector and provide no guidance at all with regard to other modes of administration.

At page 24, paragraph 3 of the response, Applicant cites MPEP § 2164.02 "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." As noted in the rejection of record and further reiterated herein above with reference to the McCluskie reference, rodent immune responses are not predictive of human immune responses and therefore it cannot be said that the rat example correlates to humans. Ample reasons have been given noting the lack of correlation.

The unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman,* 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991).

Thus, it is maintained that the specification fails to enable the full scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 12, and 14 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11, 12, and 14 are indefinite in their recitation of "decreased cognition" because "decreased" is a relative term and there is no point of reference for determining what constitutes "decreased cognition." Thus, the term "decreased cognition" is a relative term which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Therefore, the metes and bounds are not clearly set forth.

Claim 11 is indefinite in its recitation of "modulating or delaying onset of epilepsy, stroke, or decreased cognition" in the preamble because the body of the claim only requires administration of a composition and does not require that the stated goal of the preamble be achieved. Thus, the preamble is in conflict with the body of the claim.

Claims 12 and 14 are indefinite in their recitation of "ameliorating or delaying onset of epilepsy, stroke, or decreased cognition" in the preamble and to "modify the function of an NMDA receptor" in the conclusion because the preamble claim language conflicts with the conclusory claim language. Therefore, the stated goal of the preamble is not achieved.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-8, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lissin et al. (June 1998) in view of Kammesheidt et al. (1996).

Lissin et al. (June 1998) disclose an adenovirus that encodes an NMDA receptor (NR1), which is capable of being expressed in cultured hippocampal neurons (abstract;, page 7098, column 1, paragraphs 2-3; and Figure 1). Thus, the reference teaches all the limitations of the claims as written, with the exception of a pharmaceutical carrier. However, Lissin does expressly teach that important issues for future work include elucidating the NMDAR-dependent signal transduction cascade that is responsible for the decrease in the surface expression of AMPAR clusters at synapses and determining under what conditions these changes occur *in vivo*. (page 7102, sentence bridging columns 1 and 2) Accordingly, Lissin provides the explicit motivation to express epitope-tagged NMDA receptors (HA-NR1) *in vivo* for studying the conditions under which these changes in receptor surface expression occur *in vivo*. Thus, one of skill in the art would have resuspended the recombinant adenovirus in a pharmaceutical carrier suitable for *in vivo* administration, such as sterile saline. The recombinant adenovirus could then be administered *in vivo* to the rat hippocampus to study the surface expression of the epitope-tagged NMDA receptor at synapses under varying conditions, particularly examining the effects of manipulating neuronal activity on the surface expression of this receptor.

Kammesheidt et al. (1996) disclose the use of recombinant adenoviruses to transduce rat hippocampal cells *in vivo*. A recombinant adenovirus comprising the β-galactosidase gene under control of the cytomegalovirus (CMV) promoter was constructed, purified by cesium chloride banding, and resuspended in phosphate-buffered saline (PBS) for stereotactic injection into the rat hippocampus to transduce CA1 neurons (sections 2.1 and 2.2). The study demonstrated that efficient widespread transduction of CA1 *in vivo* was rapidly achievable and was sustained for more than 5 weeks (abstract and page 301, column 2, paragraph 2). The authors conclude that "the adenoviral system can be applied

to specific modulations of hippocampal proteins *in vivo* and in studying mechanisms of synaptic plasticity such as LTP and LTD" (page 304, column 1, paragraph 4). Thus, the reference shows that adenoviral vectors are useful for *in vivo* gene transfer into the rat hippocampus.

Since Lissin provides the explicit motivation to express epitope-tagged NMDA receptors *in vivo* for studying the conditions under which synaptic changes occur *in vivo*, the skilled artisan would have been motivated to take the HA-NR1 recombinant adenovirus of Lissin, purify it, and resuspend it in sterile saline as taught by Kammesheidt for *in vivo* administration into the rat hippocampus. This would have allowed the skilled artisan to study the *in vivo* effect of neuronal activity on the regulation of surface expression of NMDA receptors. The skilled artisan would have compared the *in vivo* effects with the results obtained *in vitro* in cultured hippocampal neurons. Thus, a composition comprising a pharmaceutically-acceptable carrier, such as sterile saline, and an adenovirus comprising an NMDAR gene, would have been obvious to one of skill in the art at the time of the invention, particularly given that methods for transducing rat brain cells with recombinant adenovirus were well known in the art at the time of the invention as evidenced by Kammesheidt. One of ordinary skill in the art would have anticipated a reasonable expectation of success because a recombinant adenovirus encoding an epitope-tagged NMDA receptor had already been successfully constructed in the prior art as evidenced by Lissin and methods of preparing adenoviral vectors for *in vivo* administration were well known in the art at the time of the invention as evidenced by Kammesheidt.

Therefore, the claimed invention would have been *prima facie* obvious at the time of the invention.

At page 26 of the response, Applicant asserts that the NMDA receptor (NR1) of Lissin et al. was epitope tagged with hemaglutinin (HA) and that therefore their vector differs from that of the claimed invention. On the contrary, the adenoviral vector of Lissin is identical to the vector recited in the claims. Nothing more is required. The vector of Lissin is in no way excluded from the claimed composition

merely by virtue of the epitope tag. Applicant further asserts that there is no suggestion or even a reason to assume that the HA-tagged NR1 described by Lissin et al. can be expressed *in vivo* "such that the expressed antigen elicits production of antibodies in a circulatory system of the subject, wherein the antibodies pass across a blood-brain barrier into a central nervous system upon injury." This argument has already been addressed in the Office Action of 11/30/06 at page 11. To reiterate, contrary to Applicant's assertion, it is well established that when the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent. See MPEP 2112.01 and *In re Best,* 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993), *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989). In the instant case, there is no evidence demonstrating that the claimed products are functionally different than those taught by the prior art.

At page 26 of the response, Applicant asserts that independent Claims 1 and 12 recite "a pharmaceutical acceptable carrier" and that since the Lissin reference merely describes *in vitro* experiments, there is no teaching or motivation to use a pharmaceutical acceptable carrier as required by the claims. The newly added limitation requiring "a pharmaceutical acceptable carrier" is addressed in the rejection set forth above.

Conclusion

No claims are allowable.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER